Transport and uptake of soluble gases by lung airways during transient exposure

Summary Statement of Project

Context and significance of the project

The bronchial airways provide important defences for the delicate alveolar membrane of the mammalian lung by substantially removing inhaled particulate and gaseous substances before they reach the gas exchange surface. As a result the bronchial airways are themselves prone to damage on exposure resulting in a wide range of diseases. However, there has been relatively little investigation into the transport and uptake characteristics of soluble gases in the airways in contrast to the deposition and retention of aerosols and particulate materials. This is despite the clear relevance of the topic to environmental, occupational, or short term accidental exposure to an enormous range of potentially toxic gases and vapours.

The bulk of our direct knowledge of the distribution of uptake of noxious gases within the human respiratory tract is based on observations of well known pollutants. For example sulphur dioxide has long been known to irritate the larger airways and oxidant gases such as ozone and nitrogen dioxide appear to penetrate further; they may cause pulmonary oedema, bronchopneumonia and emphysema. The fumes of many metals, *e.g.* cadmium, inhaled industrially or in cigarette smoke are known to cause lung cancers. Acetaldehyde, a constituent of cigarette smoke, is highly soluble and may be involved in the development of cancers in the conducting airways. The high local burdens of oxidants and nicotine within airway walls can also have disruptive effects on the muco-ciliary transport processes, modifying local uptake and hence toxic effects of other inhaled materials.

For obvious reasons, the toxicological effects of short term exposure to most substances in humans have to be estimated by extrapolation from animal studies. However, inhaled gases have a wide range of physical properties and their transport and uptake in the airways is extremely complex. Transport involves convection and diffusion within the airway and absorption at the wall, in a complicated branching geometry. Furthermore there are marked inter-species differences in lung geometry and overall respiratory patterns.

If inhalation toxicological models are to be extrapolated reliably from animals to humans, then all the physical processes determining transient distribution of dose within the airways need to be properly evaluated in addition to the biochemical processes within the tissues of the wall.

Objectives

The aim of the proposed work is to develop, by means of both theoretical and experimental studies, a realistic picture of soluble gas transport in the lung. In order to predict the distribution of uptake between and along individual bronchial airway paths on transient exposure with greater confidence, it will be necessary to find methods of characterising the complicated asymmetrical branching airway geometries in different species and of incorporating them in models of flow and soluble gas transport.

Methods

The approach to be adopted is strongly interdisciplinary in nature, falling between the normally funded, more conventional areas of research in toxicology and engineering fluid mechanics. Such studies are complex and require the skills of a research group with experience both within the particular areas of study and in tackling problems at the interface between mechanics and human and animal biology. Our department has a tradition of such interdisciplinary work applied to biological problems.

We propose a combined theoretical and experimental approach. Published morphometric measurements of casts of lungs from four different species will be used to formulate a mathematical model describing the essential, irregular geometry of the bronchial tree, taking direct account of the differences between species. We will then develop theoretical models for the flow and soluble gas transport in each airway in order to determine the fate of a small bolus, or volume, of inhaled soluble gas. The distance penetrated along the airways, the local absorption rates and differences in uptake between regions of the lung will be calculated. Initially, steady inspiration will be considered, later tidal breathing will be modelled.

Because the morphology and flow conditions in the bronchial tree are so complicated, the flow and transport models will have to be idealised and will need to be developed in close association with experimental studies both in physical models and excised lungs. The proposed physical model studies have been designed to parallel the theoretical studies proposed above. The general approach is designed to test the sensitivity of soluble gas uptake and dispersion to flow conditions in the lung, thereby testing the limitations of the theoretical model.

In addition to the physical model studies, we also propose to measure soluble gas transport and uptake within the bronchial airways of excised lungs of two species with lung size comparable with the human (the dog and pig). These studies will allow us to infer regional differences in gas uptake as well as giving direct information about the transport of specific gases in real lungs. The measurements will provide an important test of the theoretical model.

Project Duration: 3 years

Project Budget: The total project cost, at current prices, is approximately £215,000 including all overhead expenditure.

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